THE HEALING OF GASTRIC AND DUODENAL ULCERS WITH BISMUTH.[1]

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Bismuth was used as a medicinal agent as far back as 1786, when Oidier in Geneva recommended it as an infallible remedy for "stomach cramps;" and it has ever since asserted its place in the therapy of gastric affections. As a matter of course, Oidier used bismuth subnitrate (magisterium bismuti) quite empirically, without having any knowledge of the pathological anatomy of gastric ulcer or other gastric affections. He found that the bismuth salt had an anodyne effect upon gastric pains, and this discovery was sufficient to ensure its use, regardless of the exact pathology—which, indeed, could not in those days be clearly diagnosticated. About the middle of the nineteenth century Hannon[2] recommended bismuth as an antacid, giving, however, the preference to the subcarbonate. Oppolzer[3] likewise emphasized its antacid effect, and Bricka[4] referred particularly to the astringent effect of the drug upon the gastric mucosa.

It was left for Kussmaul to systematize the therapeutics of bismuth, following certain reflections on the pathological anatomy and physiology involved. His leading train of thought assumed this form: The irritating and painful sensations of gastric ulcer are caused by food remnants settling down at the base of the ulcer, irritating the latter as well as the exposed nerves, and thus causing acid formation and nausea. This can be easily understood as regards old and deep ulcers with elevated margins and incontractible base; and the mere passing of the gastric contents over small and superficial ulcers was held to be sufficient to cause pain. Although these food remnants can be removed by lavage, natural or artificial, this process will not prevent the constant formation of fresh deposits; so the idea suggests itself of providing a covering for the lesion which would protect it from irritation by the passing food. The same requirement follows from a consideration of the healing process. This takes place from the margins, forming granulating tissue toward the base, protecting the ulcer from irritation, and gradually closing the defect. This granulating tissue is very vulnerable, especially on the fibrous base of old and large ulcers, so that it falls an easy prey to either mechanical irritation by the ingested food or to the digestive action of the stomach. Therefore, this granulating tissue should be protected if possible—shielded from mechanical or chemical injury, just as a surgeon bandages a granulating wound in order to allow the natural healing process to take its course undisturbed.

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[1] Read before the annual meeting of the American Gastro-enterological Association at Atlantic City, N. J., June 3 and 4, 1912.

[2] Presse méd., 1850, Nos. 46 to 50.

[3] Zeitsch. d. K. K. Gesellschaft der Aerzte, Wien, January, 1857.

[4] Cited after Rodari, Experimetelles u. Klinisches z. Kenntnis der Beeinflussung der Magensaftsekretion durch Medikamente, Volkmann's Sammlung klin. Vorträge, 1908, Innere Medizin, Nos. 144 to 146.

Starting from these considerations, Kussmaul laid bismuth under tribute as the best means of securing the desired result. His expectations were realized. In many cases the pathological picture changed with surprising suddenness on the application of bismuth. Patients with old and deep ulcers, who experienced but slight relief from simple irrigations, were suddenly freed from pain; they could partake of food again, enjoyed once more an undisturbed night's rest, recovered their general health in a remarkably short time, and increased in weight. There is no longer a doubt that bismuth has a favorable effect upon the pain and the healing process in gastric and duodenal ulcer. The question now arises, how this favorable effect is to be explained, and whether Kussmaul's premises when introducing the remedy were correct.

The research work on this subject, comprising numerous clinical, anatomical, and experimental studies, has furnished proof of the fact that the protection afforded by bismuth subnitrate in gastric and duodenal ulcer is both physical and chemical.

It has been demonstrated by experiments on dogs, notably those of Matthes,[5] that a few hours after its administration bismuth is evenly distributed over the gastric wall. When the gastric contents were artificially removed, it was found that a protective layer of bismuth similar to a powder bandage had formed on the base of the ulcer. Occasional autopsy findings have shown the same effect in man. From clinical observation, too, it would appear that the bismuth deposit remains undisturbed for days upon the gastric mucosa. Fleiner[6] found that up to two or three days after the introduction of a bismuth suspension, bismuth remnants mixed with mucus could be recovered by lavage. Bismuth, as shown by the x-rays, can remain in the stomach for that length of time. This coincides with the statements of patients in regard to the length of their pain-free periods. After the first introduction of bismuth they are often free from pain during the day and the ensuing night, and sometimes longer.

All these observations have demonstrated the fact that, owing to its physical consistence, its fine distribution, and its high specific gravity, bismuth is capable of forming a layer over the ulcer which mechanically protects it from injury. Possibly, however, this effect is not purely mechanical, but due in part to chemcial action. Matthes found that bismuth, when introduced into the stomach, induced a mucous secretion, and that the protective layer was a mucó-bismuth mixture. In this process bismuth is reduced to bismuth oxide, and it may be assumed that this is the principal agent in the formation of the bismuth crust.

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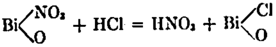
[5] Zentralbl. f. innere Med., 1894, No. 1; Beiträge z. pathol. Anatomie u. allgem. Pathol. 1893, No. 2.

[6] Münch. med. Woch., 1902, No. 23.

There is no doubt that bismuth possesses chemical properties, but it cannot yet be definitely stated whether the physical or the chemical property predominates in the relief of pain and the healing of the ulcer. The physical effect is produced by the entire quantity of bismuth introduced, whereas the chemical effect is dependent upon only a small portion of it. Bismuth subnitrate being insoluble in water is chemically inert under ordinary circumstances. A small part of the total quantity introduced in the stomach is decomposed in the acid gastric juice or duodenum, liberating nitric acid, and it is only after this process has taken place that the chemical action of the bismuth begins.

The chemical action of bismuth within the stomach and duodenum is (1) antisecretory, (2) astringent, and (3) antispetic. For the better understanding of these three bismuth effects, it is necessary to appreciate the chemical process which takes place upon the disintegration of the bismuth in the hydrochloric acid gastric contents. The decomposition of bismuth subnitrate takes place according to the following formula:



$$\mathrm{Bi}\langle{}^{\mathrm{NO_3}}_{\mathrm{O}} + \mathrm{HCl} = \mathrm{HNO_3} + \mathrm{Bi}\langle{}^{\mathrm{Cl}}_{\mathrm{O}}$$

It has been found that the effective constituent is not the bismuth oxide thus formed, but the simultaneously liberated nitric acid; the three chemical effects above mentioned are due to this factor.

The antisecretory effect of bismuth is best illustrated by an experiment of Rodari[7] upon dogs with a Pawlow fistula (Experiment 15). The experiment may be tabulated as follows:

200 c.c. of water introduced
at 7.30 A.M.

Time.	Quantity of gastric juice.
8.00 A.M.	3.2 c.c.
8.30 A.M.	2.4 c.c.
9.00 A.M.	2.0 c.c.
9.15 A.M.	1.6 c.c.
9.30 A.M.	0.8 c.c.
9.45 A.M.	0.0 c.c.

Period of secretion, 1¾ hours.
Total quantity of secretion, 10 c.c.
Total acidity, 150.

200 c.c. of water + 10 gm. bismuth
subnitrate (= 5 per cent.) introduced
at 1.30 P.M.

Time.	Quantity of gastric juice.
2.00 P.M.	2.5 c.c.
2.30 P.M.	0.2 c.c.
3.00 P.M.	0.2 c.c.
3.30 P.M.	0.0 c.c.

Period of secretion, 1½ hours.
Total quantity of secretion, 2.9 c.c.
Total acidity, 120.

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[7] Verhandlungen des Kongresses f. innere Med., 1893.

The other experiments took a similar course.

Rodari distinguishes between the following effects of bismuth subnitrate upon the gastric mucosa:

1. *Healthy Mucosa.* Typical inhibition of secretion, the quantity and probably also the quality of the secretion being reduced. This reaction of a healthy gastric mucosa is the ordinary contingency following the introduction of bismuth subnitrate.

2. *Healing.* Owing to its astringent property, bismuth is capable of producing a direct healing effect. As is well known, astringents precipitate albumin and mucus, entering into combination with the albumin and forming albuminates. This process is particularly favored in the mucous membranes. As a result of the deposition of new, firm particles (the newly formed albuminates) in the tissue interspaces, the epithelial surface is smoothed (condensed) and the size of the bloodvessels diminished. Secretion is, therefore, still further reduced, and the hyperemic conditions and attendant pains are relieved; and the fact that mucous membrane of this consistence is an unfavorable culture ground for bacteria supplies another reason for the subsidence of the inflammatory manifestations. The astringent effect of the bismuth should, however, be only superficial; the result of a deeper action would be tissue destruction or corrosion. The bismuth subnitrate having been decomposed in the acid gastric juice, it is the simultaneously liberated nitric acid which produces the astringent effect. This astringent process is one of the mildest, but may be made to last a long time, since only a small amount of bismuth is decomposed at a time, and the total quantity remains in the stomach for hours together; the dose, however, should be repeated often enough to supply the loss from disintegration. Thus it is possible, with the aid of bismuth, to maintain a uniform gently astringent process for weeks and months.

3. The *antiseptic* effect of bismuth subnitrate, illustrated in surgery by the use of this salt as a dusting powder, is applicable also in gastric and duodenal ulcer—the remedy cleansing the ulcerous base and ensuring a practically antiseptic healing of the ulcer.

The following indications have been gathered from practical experience for the application of bismuth subnitrate in practice:

The first consideration is that it is always desirable to do without any medication whatever in the treatment of gastric ulcer and duodenal ulcer. As a matter of fact, bismuth can never be regarded as a substitute for the rest cure in the treatment of ulcer. Its general purpose is to reinforce this treatment, especially when the latter fails, or when the ulcer takes a chronic course, tends to relapse, or gives rise to considerable pain; and, furthermore, in the treatment of outdoor patients. If in these cases there is hyperacidity, bismuth is so much the more indicated, for it is more effectual in hyperacid cases than in others. Bismuth is least indicated in cases marked by achylia or subacidity; in the total or comparative absence of hydrochloric acid in the stomach it cannot be decomposed, and its efficiency is restricted to the exercise of its physical properties. From this it follows that bismuth subnitrate is not to be looked upon as a specific for gastric and duodenal ulcer. Its successful application depends principally upon individualization and manner of use. The chief requirement is to have the protective layer over the ulcer large and resistant from the first, and to renew and supplement it at regular intervals. As soon as the subjective complaints are relieved, the daily bismuth dose may be tentatively reduced and, as the treatment proceeds, administered only every second day. If there should be no trouble on the day that bismuth is withheld, the intervals may be extended until finally the treatment is discontinued entirely. In consideration of what has been said about the physical and chemical action of bismuth, it is evident that it should only be administered finely suspended in a liquid medium.

As mentioned before, the practical application of bismuth has extended considerably since Kussmaul's publications on the subject, and has been further generalized and simplified by his pupil Fleiner.[8] At first, Fleiner used the following method of treatment:

The stomach being washed out, as soon as the irrigation fluid returned clear without acid reaction 10 to 20 grams of bismuth subnitrate, well mixed with 150 to 200 c.c. of tepid water, was poured through the funnel. As the tube slowly emptied itself, it was carefully withdrawn, after which the patient was immediately placed in the position corresponding to the seat of the ulcer—in the right decubitus if the ulcer were seated at the pars pylorica, and in the recumbent position if there were reason to believe that the ulcer occupied the lesser curvature.

In order not to inconvenience the stomach too much by the volume of water, Fleiner frequently left the clamped tube in the stomach for a while, until the heavy bismuth had settled, and then, before slowly withdrawing the tube, allowed part of the water to flow off.

According to his present method, the stomach tube is discarded entirely and bismuth suspensions (10 to 20 grams of bismuth subnitrate in a tumbler of warm water) are taken by mouth, in the morning, on an empty stomach, the latter having been cleansed three-quarters of an hour to an hour previously with about 150 c.c. of Carlsbad or Vichy water. The bismuth is given daily, the dose, as before mentioned, being more or less rapidly increased, reduced, or discontinued, according to the clinical course.

The quality of the bismuth preparation used is important. According to Fleiner[9] the best preparation is bismuth subnitrate which has been precipitated from a boiling hot mixture, as this is much more finely powdered than a preparation precipitated from tepid or cold fluids.

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[8] Zeitsch. f. klin. Med., 1904, vol. lii.

[9] Loc. cit.

A modification of this method consists in administering bismuth in oil by combining the bismuth treatment with Cohnheim's oil treatment — which is indeed a very practical and successful method. The doses of bismuth stated above are taken, finely suspended in olive oil, several times daily. According to Stepp,[10] bismuth suspensions in chloroform water are very efficacious:

	Gm. or c.c.
℞—Bismuthi subnitratis	3
Chloroformi	1
Aquæ destillatæ	150

M.—Sig.—One to two tablespoonfuls to be taken hourly for several weeks.

It is not unlikely that the chloroform conduces to the anodyne effect. The several methods for the application of bismuth in the treatment of gastric and duodenal ulcer have been fully described by me.[11]

There is no denying the fact that the bismuth treatment is attended with some disadvantages. Liberal and prolonged administration of bismuth is not infrequently followed by constipation, which has to be relieved either by enemas or by a combination of the bismuth with magnesium oxide. It is equally possible that, under certain circumstances, large doses of insoluble bismuth will, in passing through the intestinal tract, cause diarrhea. Nor does every stomach tolerate large quantities of bismuth. In one case bismuth has led to concrement formation in a cavity of the stomach formed by perforation of the ulcer into the pancreas (Fleiner). In a few rare cases intestinal calculi have been formed through the influence of bismuth (Wegele[12]).

There have also been cases in which the bismuth crust became so indurated and was so firmly consolidated with the ulcerous base that the ulcer underneath was prevented from healing, the crust acting like a foreign body. Cases of this kind are not very frequent, but they have occasionally been seen in autopsies and operations. Thus, Naunyn reports the case of a patient who died of gastric hemorrhage, and autopsy showed the gastric ulcer to be covered with a bismuth crust weighing about 20 grams.

A further objection, raised by Elsner, and certainly not without justification, is that the stomach may not have sufficient tonic power to bear a preparation as heavy as bismuth subnitrate administered in large doses and for a long·time. Elsner attributes the frequently observed constipation to weakness of the intestinal musculature, caused by the heavy bismuth.

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[10] Berlin. klin. Woch., 1893, p. 983.

[11] Diseases of the Stomach. Lea & Febiger, Philadelphia, 1911, pp. 442 to 446.

[12] Die Therapie der Magen und Darmerkrankungen, Jena, 1905.

All these disturbances, which will occasionally arise, should be considered when deciding upon bismuth treatment. In short, it is necessary to adapt the treatment to the individual case.

Direct failures of the bismuth treatment have been reported by Elsner,[13] Boas,[14] and Zweig.[15] These authors freely acknowledge the anodyne effect of bismuth, but do not think much of its curative effect.

Unfounded reports have been made of poisonous manifestations following the use of bismuth. Fleiner[16] states that, in 1829, Justinus Kerner published the history of a fatal poisoning by subnitrate of bismuth, but later, in 1835, the fact was established that the poisoning resulted not from bismuth, but from hydrargyrum præcipitatum album. It was this erroneous publication of Kerner's that gave bismuth a bad name, from which it has not yet entirely recovered. Other reports on poisoning by bismuth are, in all probability, attributable to the use of impure preparations, containing arsenic and lead. Chemically pure bismuth subnitrate is non-poisonous.

Boas[17] prefers the subcarbonate to the subnitrate, Hannon[18] having previously called attention to bismuth subcarbonate, as mentioned above. The subcarbonate is non-poisonous and probably has the same general effect as the subnitrate, including the antacid effect. An advantage of bismuth subcarbonate is that it colors the feces white, thereby facilitating the recognition of any coarse admixture of blood. Bismuth subnitrate, on the other hand, colors the stool black or greenish black through the formation of bismuth oxide, which may either lead timid patients to erroneously suspect hemorrhage, or conceal an actually existing hemorrhage. An objectionable feature of bismuth subcarbonate is that, on entering into combination with hydrochloric acid of the stomach, it releases a certain amount of carbon dioxide, which under certain circumstances may give rise to considerable distention of the gastric wall and the ulcer. Besides, the beneficial effect of the liberated nitric acid is lost.

Bismuth subgallate is a very acceptable substitute for bismuth subnitrate. It can be freely suspended in water and is non-toxic, but its constipating effect is greater than that of bismuth subnitrate. It can be suspended not only in water, but, as recommended by Ageron,[19] in oil to advantage.

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[13] Lehrbuch der Magenkrankheiten f. Aerzte und Studierende, 1909, Berlin.

[14] Diagnostik und Therapie der Magenkrankheiten, 1907, Part II. Leipzig.

[15] Die Therapie der Magen und Darmkrankheiten, Berlin-Wien 1907.

[16] Loc. cit. [17] Loc. cit. [18] Loc. cit.

[19] Münch. med. Woch., 1902, No. 30.